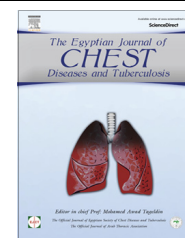




The Egyptian Society of Chest Diseases and Tuberculosis
Egyptian Journal of Chest Diseases and Tuberculosis

www.elsevier.com/locate/ejcdt
www.sciencedirect.com



ORIGINAL ARTICLE

Hypothyroidism in MDR-TB treatment – Rare occurrence but a major concern



J.S. Akshata ^{a,*}, R. Swapna ^a, Anushree Chakraborty ^a, M. Somashekar ^b,
 Shashidhar Buggi ^c

^a Dept. of Pulmonary Medicine, SDS TB Research Centre and RGICD, Bangalore, Karnataka, India

^b DRTB Centre, SDS TB Research Centre and RGICD, Bangalore, India

^c Department of CTVS, SDS TB Research Centre and RGICD, Bangalore, India

Received 11 February 2015; accepted 4 March 2015

Available online 7 April 2015

KEYWORDS

Hypothyroidism;
 MDR-TB;
 Adverse drug reaction

Abstract *Context:* To achieve good cure rate during treatment of MDR-TB, strict adherence to treatment regimen is a must. As the second line drugs have great potential to cause adverse drug reactions (ADR), identifying these adverse reactions and treating them early is major factor in preventing default. Hypothyroidism is one such ADR caused by thioamides (ethionamide, prothionamide) and paraamino salicylic acid.

Aims: To study the frequency of occurrence of hypothyroidism and its implication in MDR-TB treatment.

Settings and design: Retrospective analysis of 488 patients enrolled in our institute for MDR-TB treatment treated with standardised Cat IV treatment, as per RNTCP-PMDT guidelines.

Methods and material: Retrospective analysis of 484 (4 had hypothyroidism before treatment initiation) patients treated in our institute was done. Thyroid function test was done at baseline and repeated when indicated by symptoms during clinical follow up. Patients developing hypothyroidism (defined as TSH > 10 microIU/ml) during treatment and the reasons for same are analysed. Its implication in treatment outcome is studied.

Results: Out of the 484 study population, 19 (3.9%) had at least one documented record of TSH > 10.0 microIU/ml after treatment initiation. Median time from initiation of MDR-TB treatment to development of hypothyroidism was 153 days (range 32–441 days).

Conclusions: Occurrence of hypothyroidism is rare in MDRTB treatment. But symptomatic hypothyroidism is a major factor influencing the patient compliance towards the treatment regimen. As the drugs in regimen are effective in disease treatment, the major hindrance in achieving good cure-rate is to prevent defaulters. Identifying hypothyroidism early helps to prevent default.

© 2015 The Authors. Production and hosting by Elsevier B.V. on behalf of The Egyptian Society of Chest Diseases and Tuberculosis. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author. Tel.: +91 9535971057.

E-mail address: drjsakshata@gmail.com (J.S. Akshata).

Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

<http://dx.doi.org/10.1016/j.ejcdt.2015.03.022>

0422-7638 © 2015 The Authors. Production and hosting by Elsevier B.V. on behalf of The Egyptian Society of Chest Diseases and Tuberculosis. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Multidrug drug resistant tuberculosis (MDR-TB) treatment has effective drug regimen. The major challenge is compliance. Studies have shown that one of the important causes for default of treatment is adverse drug reactions. Drugs used for MDR-TB treatment have a great potential to cause adverse effects [1,2]. They range from mild gastrointestinal disturbances, arthralgia to major psychosis, suicidal tendencies and severe hypothyroidism [3].

Hypothyroidism is a known side effect of thioamides (TA)–Ethionamide (ETH), Prothionamide (PTH) and Para aminosalicic acid (PAS) [4–7]. Hypothyroidism has vague and non specific symptoms which can be easily missed. Various studies have reported hypothyroidism varying from 3.5% to as high as 69% [3,8,9]. Present study was done to ascertain the rate of occurrence of hypothyroidism in MDR-TB patients treated with standardised cat-IV regimen under programmatic management of drug resistant tuberculosis (PMDT).

Materials and methods

Retrospective cohort study was done in SDS Tuberculosis Research Centre and Rajiv Gandhi Institute of Chest Diseases, Bangalore.

Inclusion criteria: all patients of sputum culture confirmed MDR-TB enrolled from August 2011 to March 2014.

Exclusion criteria: patients with diagnosed hypothyroidism or those with pre treatment TSH > 10 microIU/mL.

All confirmed MDR-TB patients were admitted for pre-treatment evaluation and treatment initiation. As per the national guidelines thyroid profile was done prior to initiation. Patients were started on standardised cat IV regimen which includes Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol, Cycloserine for 6–9 months and Levofloxacin, Ethionamide, Ethambutol and Cycloserine for 18 months. PAS was used as a substitute drug in case of major adverse effect or initial resistance to any of second line drugs. After 10–30 days of initial hospitalisation, patients continued community based treatment at peripheral centres. As per the PMDT guidelines, they were regularly followed up clinically. Thyroid function tests are repeated on clinician suspicion of hypothyroidism. Thyroid stimulating hormone (TSH) was measured from blood samples using ultra-sensitive sandwich chemiluminescent assay. Data were collected by reviewing patients' case records, treatment cards, registers and reports sent online. Hypothyroidism is defined as at least one measure of TSH > 10.0 microIU/ml after initiation of MDR-TB treatment. Data thus collected were analysed.

Results

From August 2011 till March 2014, 488 patients enrolled for MDR-TB treatment in SDSTRC and RGICD, Bangalore. All patients had thyroid profile before initiation of treatment. 4 of them had TSH level more than 10.0 microIU/ml; hence they were excluded from the study. Out of the 484 study population, 19 (3.9%) had at least one documented record of TSH > 10.0 microIU/ml after treatment initiation. The clinical profile of those 19 patients is shown in Table 1.

Mean TSH level of patients who developed hypothyroidism was 12.86 microIU/ml. Of the 19 patients who developed hypothyroidism, 17 received only ethionamide and 2 of them received both Ethionamide and PAS. Median time from initiation of MDR-TB treatment to development of hypothyroidism was 153 days (range 32–441 days). All patients with TSH > 10 microIU/ml were initiated on levothyroxine 25–100 µm daily depending on body weight and TSH levels irrespective of symptoms. TSH levels were monitored regularly and levothyroxine dose adjusted accordingly. MDR-TB treatment drugs were not modified in any of these patients.

Out of these 19 patients who developed hypothyroidisms 5 were declared cured, 4 died and 10 are still on treatment. Among 4 who died 1 committed suicide, 2 died of non TB causes and 1 died after diagnosed as XDR-TB (Table 2).

Discussion

Treatment of MDR-TB is challenging. Long duration of treatment, multiple drug usage and severe drug reactions are limitations. Many studies have reported adverse drug reactions. Frequency of such adverse drug reactions ranged from 57% to 80% in various studies done in India and other countries [10,11]. These adverse reactions are varied. Some are minor and few are major. But these major adverse reactions are hindrance for strict adherence of treatment leading to unfavourable outcome.

Symptomatic hypothyroidism can be disturbing in day to day life. After the introduction of cat IV, treatment of MDR-TB is standardised and drugs used is same in all patients. The frequency of adverse drugs reactions with cat IV, particularly the occurrence of hypothyroidism is not studied carefully. Few studies done in different countries showed the occurrence of hypothyroidism varying from as low as 3.5% to as high as 69% [3,8,9].

In our study, rate of hypothyroidism after MDR-TB treatment was 3.9%. This is in contrary to studies from Egypt [12] (39.5%), Botswana [8] (16.2%), Russia [13] (17.2%), Peru [14] (10%) and Lesotho [9] (69%). 3.5% hypothyroidism was reported in one study evaluating adverse drug reactions collectively from five DOTS-Plus centres [3]. Studies with a high rate of hypothyroidism had both thioamides (ETH/PTH) and PAS in the treatment regimen.

Table 1 Clinical profile of patients.

		Number/Mean (range)
Age (yrs)		31.7 (14–55)
Sex	Male	10
	Female	9
HIV/on ART		Nil
Drugs	ETH	17
	PAS only	Nil
	ETH + PAS	2
TSH	Baseline	4.11 (0.01–8) microIU/ml
	At diagnosis	12.86 (10.12–30.67) microIU/ml)
Median time		153 days (32–441 days)

Table 2 Treatment outcome in patients who developed hypothyroidism.

Cured	5
Death	4
On treatment	10

Patients in our study received only ETH. PAS was used as a reserve drug. Out of the 19 patients who developed hypothyroidism, only 2 received both ETH and PAS. In 1 patient kanamycin was replaced with PAS due to nephrotoxicity and in another patient Levofloxacin was replaced with Moxifloxacin and PAS, as he showed initial resistance to Levofloxacin.

Mean age of patients who developed hypothyroidism was 31.7 yrs in our study as opposed to 40 yrs in the study done in Botswana [8]. However the range was from 14 to 55 yrs. This showed no preponderance to any specific age. Male or female preponderance was not seen in our study similar to the study done in Lesotho where male sex was not statistically associated with hypothyroidism [9]. None of our patients had HIV seropositive status and so were not on ART. Use of Stavudine has been associated with the development of subclinical hypothyroidism [15].

Baseline TSH of patients who developed hypothyroidism ranged from 0.01 to 8 microIU/mL (mean 4.11 microIU/mL) but elevated to > 10 microIU/mL after more than 1 month of treatment. This implies that hypothyroidism was induced by MDR-TB treatment rather than a pre existing condition. Elevated TSH levels varied from 10.12 to 30.67 microIU/mL (mean 12.86 microIU/mL). Study in Lesotho reported that 77.5% of 129 patients who developed hypothyroidism had TSH > 20 microIU/mL in contrast to our study where only 2 (10.5%) had TSH > 20 microIU/mL [9].

Few studies monitored TSH regularly during treatment like every 2 months or at 6 and 12 months [9,13]. These studies reported high rate (17.2%, 69%) of hypothyroidism. 2 studies reporting 10% and 16.2% were measuring TSH as and when indicated [8,14]. In our study TSH was repeated after baseline test based on clinicians' decision and not routinely. Hypothyroidism has non-specific symptoms (fatigue, cold intolerance, dry skin, constipation, unexplained weight gain, menstrual disturbances, depression etc.) which may be easily missed by the treating clinicians or may be confused with the side effects of other second line drugs. WHO guidelines recommend screening for hypothyroidism at 6–9 months after initiation of MDR-TB treatment [16].

Median time to hypothyroidism was found to be 153 days (range 32–441 days) in our study. Other studies had median time between 93 and 300 days [8,9,13,14]. Only 3 (15.7%) developed hypothyroidism between 2 and 3 months whereas majority became symptomatic after 3 months of treatment. The 2 patients who were on both ETH and PAS had elevated TSH level of 11–12 microIU/mL; 1 after 32 days and the other after 441 days of treatment. Whether combined ETH and PAS synergistically leads to hypothyroidism early in the course of treatment could not be ascertained. Studies which used both ETH and PAS in the treatment regimen had median time to hypothyroidism between 93 and 120 days [9,13].

Patients developing hypothyroidism continued the same treatment regimen with favourable outcome. None of the patients diagnosed with hypothyroidism defaulted. The fact that 1 patient committed suicide needs attention. Suicidal tendencies are known side effect of cycloserine but depression is also a symptom of hypothyroidism. Delay in identifying the same could be a reason.

Our study had several limitations. Being a retrospective study data might have been lost. Patients were non compliant for regular clinical monitoring. Subtle symptoms of hypothyroidism may have been missed by the clinicians as TSH was not monitored regularly leading to under-diagnosis. Hence a prospective study is needed to ascertain the real magnitude of hypothyroidism.

Conclusion

Hypothyroidism rate was low in our cohort. The diagnosed cases may represent only the tip of the ice berg. Unrecognised hypothyroidism may lead to unfavourable outcome like death or default in MDR-TB treatment. Prompt recognition and treatment of hypothyroidism can lead to adherence of treatment with successful outcome. Monitoring with TSH levels even in asymptomatic cases at regular intervals like 3 months and again between 6 and 9 months of MDR-TB treatment may be considered optimal.

Conflict of interest

None declared.

References

- [1] A. Van Deun, M.A. Salim, A.P. Das, I. Bastian, F. Portaels, Result of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh, *Int. J. Tuberc. Lung Dis.* 8 (5) (2004 May) 560–567.
- [2] Aleyamma Thomas, Rajeswari Ramachandran, Fathima Rehaman, K. Jaggarajamma, T. Santha, N. Selvakumar, et al, Management of multi drug resistance tuberculosis in the field: tuberculosis research centre experience, *Indian J. Tuberc.* 54 (2007) 117–124.
- [3] E. Nathanson, R. Gupta, P. Huamani, et al, Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative, *Int. J. Tuberc. Lung Dis.* 8 (2004) 1382–1384.
- [4] D. Drucker, M.C. Eggo, I.E. Salit, G.N. Burrow, Ethionamide induced goitrous hypothyroidism, *Ann. Intern. Med.* 100 (1984) 837–839.
- [5] S. Thee, E.W. Zöllner, M. Willemse, A.C. Hesselting, K. Magdorf, H.S. Schaaf, Abnormal thyroid function tests in children on ethionamide treatment, *Int. J. Tuberc. Lung Dis.* 15 (2011) 1191–1193.
- [6] D.A. Edwards, E.N. Rowlands, W.R. Trotter, The mechanism of the goitrogenic action of p-aminosalicylic acid, *Lancet* 264 (1954) 1051–1052.
- [7] T. Munkner, Studies on goitre due to para-aminosalicylic acid, *Scand. J. Respir. Dis.* 50 (1969) 212–226.
- [8] Chawangwa Modongo, Nicola M. Zetola, Prevalence of hypothyroidism among MDR-TB patients in Botswana, *Int. J. Tuberc. Lung Dis.* (2012) 1561–1562.
- [9] H. Satti, A. Mafukidze, P.L. Jooste, M.M. McLaughlin, P.E. Farmer, K.J. Seung, High rate of hypothyroidism among

- patients treated for multidrug-resistant tuberculosis in Lesotho, *Int. J. Tuberc. Lung Dis.* 16 (2012) 468–472.
- [10] K. Kapadia Vishakha, B. Tripathi Sanjay, Analysis of 63 patients of MDR TB on DOTS plus regimen: An LG hospital, TB Unit, Ahmedabad experience, *Gujarat Med. J.* 68 (2) (Dec 2013) 52–57.
- [11] T.Q. Jacobs, A. Ross, Adverse effects profile of multidrug-resistant tuberculosis treatment, *S. Afr. Family Pract.* 54 (6) (2012) 531–539.
- [12] Ibrahim I. Elmahallawy, Ramadan M. Bakr, Ali A. Mabrouk, et al, Treatment outcomes among patients with multi-drug resistant tuberculosis in Abbassia Chest Hospital from July 2006 to June 2010, Egypt. *J. Chest Dis. Tuberc.* 61 (2012) 337–342.
- [13] S.S. Shin, A.D. Pasechnikov, I.Y. Gelmanova, G.G. Peremitin, A.K. Strelis, S. Mishustin, et al, Adverse reactions among patients being treated for MDR-TB in Tomsk Russia, *Int. J. Tuberc. Lung Dis.* 11 (12) (2007) 1314–1320.
- [14] J.J. Furin, C.D. Mitnick, S.S. Shin, J. Bayona, M.C. Becerra, J.M. Singler, et al, Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis, *Int. J. Tuberc. Lung Dis.* 5 (7) (2001) 648–655.
- [15] G. Madeddu, A. Spanu, F. Chessa, et al, Thyroid function in human immunodeficiency virus patients treated with highly active antiretroviral therapy (HAART): a longitudinal study, *Clin. Endocrinol. (Oxf)* 64 (2006) 375–383.
- [16] World Health Organization, Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. WHO/HTM/TB/2008.402. Geneva, Switzerland, WHO, 2008.